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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	25

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/508,095	Applicant(s) ZUCHT ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The previous Office Action (Advisory Action) mailed August 4, 2003 has been vacated because the mixed-up filing date of the amendment filed March 28, 2003.

Status of the Claims

2. Claims 3 and 18-29 are pending.

Applicants' amendment filed March 28, 2003 (Paper No. 23) is acknowledged and applicants' response has been fully considered. Claims 13-17 have been cancelled, claim 3 remains withdrawn from consideration, and new claims 18-29 have been added. Applicant has elected SEQ ID NO:22 for examination in Paper No. 11. Upon consideration, SEQ ID NOs: 17 and 19 will also be included for examination. Thus, claims 18-29 and SEQ ID NOs:17, 19 and 22 are examined.

Objection Withdrawn

3. The previous objection of claim 14 is withdrawn in view of applicants' cancellation of the claim.

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 13-17 under 35 U.S.C.112, first and second paragraphs, is withdrawn in view of applicants' cancellation of the claim.

Informalities

The disclosure is objected to because of the following informalities:

5. The specification is objected to for "R_1, R_3 independently represents NH_2" and "R_2, R_4 independently represents COOH, $CONH_2$" (page 3) since each amino acid in the peptide (HN-CH(R)-CO) has already contained the amino (NH) and carbonyl (CO) groups. It is incorrect to

cite "R_1, R_3 independently represents NH_2" for N-terminal end of the peptide, and "R_2, R_4 independently represents COOH, $CONH_2$" for C-terminal end of the peptide, it should be written as "R_1, R_3 independently represents H" and "R_2, R_4 independently represents OH, NH_2". Appropriate correction is required.

Claim Objections

6. Claims 18 and 19 are objected to because the claim contains recitation of non-elected sequences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide with a defined sequence such as SEQ ID NO:17 or 19 obtained from cow or human milk via a process of proteolytic cleavage and purification, and having bifidogenic properties; a composition comprising the peptide; and a method of obtaining the peptide; or the peptide of human milk kappa-casein (182 amino acids) as indicated in the prior art, does not reasonably provide enablement for a peptide obtained from cow or human milk via a process of proteolytic cleavage and purification, or, the N-terminal modified derivative of the peptide, which has bifidogenic property, wherein the amino acid sequence of the peptide is not defined; a composition comprising the peptide; and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria, comprising administering the peptide to an individual. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-29 are directed to peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, the N-terminal modified derivatives thereof, which have bifidogenic properties (claims 18, 19, 22 and 23), a method of obtaining these peptides (claims 20 and 21), a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria (claims 24-27), and a composition containing the peptide (claims 28 and 29). The specification, however, only discloses cursory conclusions (pages 1-14) without data supporting the findings, which state that peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, or, their amidated, acetylated, sulfated, phosphorylated, glycosylated or oxidized derivatives or fragments thereof, would have bifidogenic properties (pages 1-2), and some sequences are listed as preferable embodiments (page 3). There are no indicia that the present application enables the full scope in view of peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, and the derivative thereof as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, and N-modified derivatives of the peptides, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification only demonstrates certain peptides such as SEQ ID NOs: 17 (casein K-63-117) and 19 (neutrophile lactoferrin 20-67), and the corresponding oxidation product exhibit bifidogenic activity (Example 1, page 8). There are no other working examples indicating the claimed variants or methods in association with the claimed invention.

(3). The state of the prior art and relative skill of those in the art:

Mukerji *et al.* (WO 98/08269, March 1996) teach human kappa-casein having 182 amino acids comprises the peptide of SEQ ID NO:17; and Proulx et al. (Lait 74, 139-152 (1994)) indicate the casein hydrolysates produced by three proteolytic enzymes have bifidogenic activity. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of N-modified derivatives of the peptides, and the treating conditions for promoting the growth of bifidobacteria in individual using the specific peptide and the effect of the peptide to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, and the derivative thereof, which have bifidogenic

properties, a method of obtaining these peptides, and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria. The specification indicates the peptides isolated and purified from cow milk or human milk can promote the growth of desired bacteria such as bifidobacteria more than that of other bacteria or by selectively inhibiting the undesired bacteria, which is defined as "bifidogenic" (page 3, first paragraph), and the peptide can be contained in medicaments or in food, and further asserts the peptides are suitable for treating diseases caused by various microorganisms (pages 4-5). The Examples have only indicated the isolation and purification of certain peptides (SEQ ID Nos:17 and 19) having bifidogenic properties (Example 1, page 8), the method of monitoring the growth-regulating activity on *E. coli* (Example 2), the method of monitoring the growth-regulating activity on *Bifidobacterium bifidum* (Example 3), and a formula to define bifidogenic activity (Example 4). However, the specification has not demonstrated the peptides other than SEQ ID NO:17 and 19 have bifidogenic property, nor has identified any N-terminal modified derivative having the bifidogenic property. There are no working examples indicating the bifidogenic activities of the peptides other than SEQ ID NOs:17 and 19 and the N-modified derivatives of peptides obtained from cow or human milk via a process of proteolytic cleavage and purification. Furthermore, there is no *in vitro* or *in vivo* data indicating the peptide or the derivative thereof is effective in promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in individual. Therefore, it is necessary to have additional guidance on the identity of the N-modified derivatives of the peptides obtained from cow or human milk, and the treating conditions such as dose for promoting the growth of bifidobacteria in individual, and to carry out further experimentation to assess the in vivo effect of the peptides with bifidogenic property.

(5). Predictability or unpredictability of the art:

The claims encompass many peptide variants and the treating conditions such as the dose for various peptides and the effects of the peptides are not described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not demonstrated the use and the effects of these peptide variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the bifidogenic effect of the claimed invention.

8. Claims 20-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-29 are directed to peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, the N-terminal modified derivative thereof, which have bifidogenic properties, a method of obtaining these peptides, and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria. The specification indicates that peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, or, their amidated, acetylated, sulfated, phosphorylated, glycosylated or

oxidized derivatives or fragments thereof, would have bifidogenic properties (pages 1-2), and some sequences are listed as preferable embodiments (page 3). The specification further asserts that SEQ ID NOs: 17 (casein K-63-117) and 19 (neutrophile lactoferrin 20-67), and the oxidation product exhibit bifidogenic activity (Example 1, page 8). However, the specification has not identified a specific N-modified derivative of a bifidogenic peptide. There is no disclosure indicating the N-terminal modified derivatives of the peptides are functional. Without guidance on structure to function/activity, one skilled in the art would not know which region or residue of the peptide is essential for function/activity and how to identify a functional peptide. The lack of a structure to function/activity relationship and the lack of representative species for the N-terminal modified derivatives of the peptides having bifidogenic properties as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

In response, applicants indicate the provided references have shown how to make N-modified peptide, e.g., by amidation, phosphorylation; and the determination of which N-modified peptide having bifidogenic activity does not involve undue experimentation (pages 9-11 of the response); Regarding the treatment of disease in accordance with the invention, applicants indicate the treating condition such as dose has been described in the specification, and it is not necessary to describe all embodiments in the specification, and the fragments have been removed (pages 12-13 of the response); and the first paragraph of 112 contains no requirement for a structural disclosure, a description in functional terms can satisfy the enablement requirement (page 14 of the response). The response has been fully considered,

however, the argument is found persuasive because the specification has not demonstrated a specific peptide other than SEQ ID NOs:17 and 19 or the N-modified peptides possess the bifidogenic property, although the term "fragments" has been removed from the claims; the references provided by applicant do not provide all the teachings required for the claimed invention, e.g., the reference does not teach how to make N-terminal phosphorylated or amidated peptide, the references only indicate a peptide with Tyr or Ser can be phosphorlated at the side chain; Regarding the treatment, a dose range has been cited in the specification (page 5, paragraph 5), however, there is no in vitro or in vivo data indicating a specific peptide within this dose range is effective in the treatment. Furhtermore, the function of the peptide depends on its structure, without identification of the structure of the peptide, and providing the correlation of structure to function/activity and representative species, one skilled in the art would not know how to identify a functional peptide. The claims encompass many peptide variants, while the teachings regarding the use and the effects of the peptides are not described in the specification as indicated in the section above. Therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the peptides obtained from cow or human milk via a process of proteolytic cleavage and purification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 18, 24 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 18, 24 and 29 are indefinite because of the use of the term "R_1, R_3 independently represents NH_2" or "R_2, R_4 independently represents COOH, $CONH_2$". It is not clear what group the N-terminal or C-terminal end of the peptide has since each amino acid (HN-CH(R)-CO) in the peptide has already contained the amino (NH) and carbonyl (CO) groups, e.g., if N-terminal of peptide is R_1-A, and R_1 =NH_2, R_1-A would be H_2N-NH-$CH(CH_3)CO$-, which is not a correct structure.

In response, applicants indicate "NH_2" and "COOH" at the amino and carboxyl ends is well known and used in the amino acid sequence (e.g., NH_2-Gly-Asp-Phe-Arg-Gly-COOH) and is illustrated in Stryer, Biochemistry (1981), pages 23-24 (pages 17-18 of the response). The argument is not persuasive because the formula of amino acid in the peptide already includes both NH and CO group as indicated above, e.g., if "R_1, R_3 independently represents NH_2" or "R_2, R_4 independently represents COOH, $CONH_2$" is used, then the sequence of NH_2-Gly-Asp-Phe-Arg-Gly-COOH would be H_2N-NH-CH_2CO-Asp-Phe-Arg-NH-CH_2CO-COOH, which conatin extra NH and CO groups in the formula. Please see Voet & Voet "Biochemistry", pages 112-113 for clarification (attached in the previous Office Action).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 18 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Mukerji *et al.* (WO 98/08269, march 1996).

Mukerji *et al.* teach human kappa-casein (Fig. 8, SEQ ID NO:1 of WO 98/08269) and a pharmaceutical composition comprising human kappa-casein for treating an infection of a mammalian cell caused by human rotavirus (page 4, third paragraph; claim 3 at page 28; Examples 4 and 5; claim 28). Human kappa-casein having 182 amino acids comprises the core sequence of SEQ ID NO:17 (55 amino acids) and meets the criteria of R_1 and R_2 (See sequence match), thus, it would be expected to have bifidogenic properties (claim 18).

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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August 11, 2003